II. REMARKS

Summary Of Record Of Interview

A personal interview was held on October 29, 2004, between the examiner, Michael Meller, the applicant, Professor Mark Pepys, and the applicant's representatives, Charles Rories and Thomas Cawley, Jr. Prior to the interview, a draft version of the present amendment and copies of the Iversen and Borman references were provided to the examiner.

During the course of the interview, the applicant explained it was that his own work that served as the groundwork for the invention disclosed in the Hertel patent, and that at the time the invention described in the Hertel patent was invented, the only physiological activity considered for compounds having the chemical formula disclosed in the Hertel patent was inhibition of the binding of SAP to amyloid fibrils. Dr. Pepys explained that at the time the invention of the Hertel patent was made, it was completely unforeseen that a multi-ligand compound having the chemical formula disclosed in the Hertel patent could cause depletion of a ligand-binding protein such as SAP, from a patient's plasma. The applicant directed the examiner's attention to the Iversen and Borman references, as evidence that at the time the presently claimed invention was made, scientists in the field regarded the applicant's work as an original and significant advance.

The applicant's representatives stated that amendment of the claims to specify a step of monitoring the clearance of the disease-associated protein population from the subject's plasma appears to distinguish the claimed invention from the prior art. The examiner agreed to consider the point, and stated such an amendment would necessitate review of the prior art references to see if they described or suggested the proposed step.

The examiner also suggested the claims be amended to provide additional description of the subject and the pathology being treated.

The applicant and his representatives greatly appreciate the examiner's willingness to hold the interview and to consider the applicant's proposed amendments and arguments for withdrawal of the outstanding rejections.

Preliminary Remarks

Non-elected claims 1-17 are canceled, claims 18-35 are amended, and new claims 36-43 are added.

Independent claims 18, 24 and 26 are amended to specify that the claimed method is a method for the depletion of a disease-associated protein population from the plasma of a subject in need of such treatment, as described, for example, on pages 1-3 of the application.

Claims 18, 24 and 26 are also amended to include a step of monitoring the clearance of the disease-associated protein population from the subject's plasma, as described in the specification; e.g., at the bottom of page 15.

Claim 18 is further amended to specify that the claimed method comprises binding of at least two of the ligands by the ligand binding sites of the proteins in the plasma, forming thereby a complex between the agent and a plurality of the proteins, wherein the complex is abnormal to the subject; whereby the complex is caused to be identified by the physiological mechanisms of the subject and cleared from the plasma, as described throughout the specification; for example, in the last two paragraphs of page 5, bridging to page 6.

Claim 29 is amended to be dependent on claim 26, and to specify that the amyloidogenic protein is selected from the group consisting of amyloidogenic proteins disclosed in the application (e.g, on page 1).

Claim 31 is amended by deleting reference to a particular type of glycosidic linkage in the ligand; and new claims 36-39, which depend on claim 31, specify the particular glycosidic linkage described on page 26.

New claims 40-47 specify that the claimed method effects clearance from a subject's plasma of the specific types of disease-associated proteins disclosed in the specification (for example, see on page 1).

Claims 1-35 are also amended to begin with an indefinite article ("a") or a definite article ("the").

Patentability Remarks

Rejections under 35 U.S.C. §102

Claims 18-35 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Hertel *et al.*, Nitecki et al., Watasuka et al., or WO 98/50420, on the grounds that the references teach that the claimed compound is administered to a patient (as stated in the

official action dated March 5, 2003), and the claims only require that a non-proteinaceous agent be administered to a subject (as stated in the official action dated November 28, 2003).

The applicants respectfully traverse the rejection of the claims as being anticipated by the cited prior art references, and submit that the invention claimed in this application is entirely novel, and that there is no relevant prior art.

The present claims are directed to a novel method for depleting a disease-associated protein population from the plasma of a subject in need of such treatment.

The claimed method comprises administering an agent that comprises a plurality of ligands that form complexes with a plurality of the unwanted proteins (page 3, paragraph 3). These complexes are recognized by the subject's body and are cleared and destroyed by the body's physiological mechanisms. The claimed method also expressly includes the step of monitoring the clearance of the disease-associated protein population from the subject's plasma. Neither Hertel et al. nor the other cited prior art described a method than can even remotely be represented as suggesting or implying the present invention.

The ability of antibodies and other biological macromolecules to bind to their respective specific ligands, whether these are low molecular weight substances or biological macromolecules, is well known. Such binding can modify the handling and fate of the bound substances in various ways. However, prior to the present invention, nobody had suspected or imagined that palindromic or multivalent low molecular weight ligands could be used as therapeutic agents to cause the body to swiftly and totally eliminate pathogenic target proteins from the circulating plasma. The present invention provides a method wherein specific low molecular weight non-protein chemical compounds that bear ligands recognized by binding sites present on circulating plasma proteins are administered to effect removal of targeted proteins from the plasma. The target proteins are of pathogenetic importance, being responsible for causing or exacerbating disease. The low molecular weight compounds that are useful as drugs for prevention and treatment of disease bear at least two ligand groups per molecule, and these may be identical or they may be different. There may also be more than two ligand groups per molecule, that may be identical or of two different types. When they are introduced into the body, these drugs are bound by the target proteins and cross link them in pairs or in larger numbers by virtue of the drugs containing at least two ligand groups that are recognized by the target proteins. The drug-protein complexes formed in this way are protein aggregates that are not normally present in the body.

These abnormal aggregates are detected and promptly removed from the circulation by cells in the body specialized for this task, particularly in the liver. This leads to rapid depletion of the target protein or proteins from the circulation, so that they can no longer cause disease, and there is then corresponding clinical benefit.

Hertel et al. does not disclose the claimed therapeutic method. Hertel et al. states that the disclosed D-proline derivatives are useful for treating or preventing amyloidosis (col. 3, line 66, to col. 4, line 1). Hertel et al. provides little additional description regarding how the disclosed compounds are used. The application states that a

> "common pathological feature [of amyloidosis] is extracellular deposition of so called amyloid proteins in B-structured fibers and the same staining characteristics." (col. 4, lines 20-22),

and that

> "Serum amyloid P component (SAP) is a normal plasma protein and the precursor of amyloid [P] component, a universal constituent of the abnormal tissue deposits in amyloidosis. It is resistant to proteases and therefore plays a key role in the persistance of amyloid in vivo. **For therapy pharmaceutically active compounds have to be found which would prevent the interaction of SAP with amyloid fibrils.** This interaction has been demonstrated to be a protein fiber interaction, rather than an interaction with more general fiber components such as glycosaminoglycans. SAP consists as a pentamer of 5 identical non-covalently associated subunits. Two pentamers can non-covalently associate to a decamer with the two pentameric disk-like rings interacting face to face. SAP is a calcium-dependent ligand binding protein. It is produced and degraded exclusively in hepatocytes and extremely stabile outside the liver."
>
> "The participation of SAP in the pathogenesis of amyloidosis in vivo confirms that **inhibition of binding to amyloid fibrils is an attractive therapeutic target** in a range of serious human diseases." (col. 4, lines 23-42, emphasis added).

The Hertel et al. reference clearly describes the D-proline derivatives disclosed therein as compounds that derive their therapeutic activity from their ability to inhibit the binding of SAP to amyloid fibrils. The formulas of the compounds disclosed by Hertel et al. include many compounds that do not have any therapeutic activity. One of skill in the art would therefore look to the teachings of Hertel et al. for guidance in determining which of the thousands of

compounds encompassed by the disclosed formulas have the desired activity. From the description of the invention given in the application of Hertel et al., a person of skill in the art would reasonably infer that the disclosed D-proline derivatives of the invention of Hertel et al. are compounds that inhibit the binding of SAP to amyloid fibrils and treat or prevent amyloidosis. Accordingly, one of skill in the art would reasonably regard Hertel et al. as teaching that compounds of the disclosed formulas that have the desired activity can be identified by screening to identify compounds that inhibit the binding of SAP to amyloid fibrils under physiological conditions with sufficient efficacy that they are expected to inhibit deposition of SAP on insoluble amyloid fibrils in vivo. Compounds that inhibit the binding of SAP to amyloid fibrils as described in Hertel et al. include compounds that bind only a single SAP pentamer and do not clear targeted proteins from the plasma of a treated individual.

In contrast, to the methods suggested by Hertel et al., the present claims are specifically directed to a method for depleting an unwanted protein population from the plasma of a subject, and the multi-ligand compounds that are administered according to the claimed invention are expressly described as being capable of being bound by ligand binding sites present on the proteins, binding of at least two of the ligands by the ligand binding sites of the proteins in the plasma; forming thereby a complex between the agent and a plurality of the proteins, wherein the complex is abnormal to the subject; and causing the complex to be identified by the physiological mechanisms of the subject and cleared from the plasma. **Furthermore, the claimed method includes a step of monitoring the clearance of the disease-associated protein population from the subject's plasma.** The method of the present claims is neither described nor suggested by the inhibitory method disclosed by Hertel et al.

The claimed invention also is not anticipated under 35 U.S.C. §102, under a presumption that the claimed method is inherent in the methods suggested by Hertel et al. A compound that is disclosed by Hertel et al. is used in the present invention as an example. It belongs to the extensive family of small molecules that are suitable for use in the present invention which share the obligatory feature of having two or more ligand groups that are bound by one or more target proteins, cross link them, and form complexes that the body perceives as abnormal and rapidly eliminates from the plasma. For the claimed invention to be anticipated under 35 U.S.C. § 102, there must be identity of invention. "Identity of invention is a question of fact, ... and one who seeks such a finding must show that each element of the claim in issue is found, either expressly described or under principles of inherency, in a single prior art reference, or that the claimed

invention was previously known or embodied in a single prior art device or practice." See Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538-39, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983), citing Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 771, 218 U.S.P.Q. (BNA) 781, 789 (Fed. Cir. 1983). The presently claimed invention unequivocally includes clearance or removal of an unwanted protein from the plasma, and may be practiced with compounds which are such poor inhibitors of the binding of SAP to amyloid fibrils that they are unsuitable for use as therapeutic inhibitors according to the teaching of Hertel et al. Moreover, the claimed method also comprises monitoring the clearance of the disease-associated protein population from the subject's plasma. The claimed method for clearing a target protein from plasma is therefore neither suggested by nor inherent to the inhibitory method disclosed by Hertel et al.

The present claims were also rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Nitecki et al., Watasuka et al., or WO 98/50420.

Nitecki et al. describe using analogs and derivatives of succinylacetone that operate as immunosuppressive agents (see col. 2, line 60, to col. 3, line 25), and measuring DNA synthesis by lymphocytes to assay for immunosuppression (col. 9, lines 3-62).

Watasuka et al. describe 6-keto-prostaglandin derivatives that possess cytoprotective activity (see col. 14, lines 57-64), and cyclodextrin clathrates of such compounds. However, multiple 6-keto-prostaglandin derivatives that are contained within the interstices of a cyclodextrin clathrate are not covalently co-linked ligands as specified by the current claims; and Watasuka et al. does not describe the clearance of a disease-associated protein population from a subject's plasma.

WO 98/50420 describes compounds that bind and inhibit serine proteases such as thrombin, factor VIIa/tissue factor, and factor Xa (see p. 3, lines 12-13), and it describes assaying to detect the inhibition of the targeted proteases by measuring the concentration of products generated by the action of the targeted proteases on test substrates.

Like Hertel et al., the Nitecki et al., Watasuka et al., and WO 98/50420 references failed to describe or suggest the claimed method comprising administering low molecular weight non-protein chemical compounds that bear a plurality of covalently co-linked ligands recognized by binding sites present on targeted proteins circulating in the plasma proteins and effect clearance of the targeted proteins from the plasma. The cited references also failed to suggest a method comprising a step of monitoring the clearance of the disease-associated protein population from the subject's plasma. The possibility that the

claimed invention would operate successfully to clear targeted proteins from the plasma was not suspected or envisioned by the prior art, nor was it investigated. The present invention involves a mechanism of molecular interaction and biological effect that are separate and unrelated to the therapeutic methods described in the prior art references.

After submission of the present application, scientific work relating to the claimed invention was published in a major article in the journal *Nature* (Pepys *et al.*, "Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis", *Nature* 417, 254-259, 2002; see reference IR1 filed Sept. 5, 2003), which is considered by many to be the most prestigious scientific journal in the world, submissions to which are subjected to extremely rigorous refereeing by world leading scientific reviewers. The paper by Pepys *et al.* describing the claimed invention, including a claim for the originality of the work, was not only accepted by the journal's editors, but was accompanied on publication by a *"News and Views"* commentary by Dr. Les Iversen, who prior to writing the article had been Head of Drug Discovery for Neuroscience at Merck Pharmaceutical Corp. for 11 years, and may be regarded as an expert in matters of drug originality. Dr. Iversen described the work by Pepys *et al.* corresponding to the claimed invention as "a new pharmacological approach to treating human amyloid diseases;" and stated that "this new approach offers great promise for treating both peripheral amyloid disorders and possibly, Alzheimer's disease." (Iversen, "Amyloid diseases: Small drugs lead the attack," Nature, 2002, 414:231-233; copy attached). The scientific discoveries corresponding to the claimed invention were also recognized in 2002 by the American Chemical Society as one of the medicinal chemistry highlights of 2002 (see Borman, S., "Chemistry Highlights 2002, Medicinal and Combinatorial Chemistry," Chem. Eng. News, 2002, 80:37-38). The recognition of the originality of scientific advances corresponding to the claimed invention by the editors of *Nature*, by Dr. Iversen, and by the American Chemical Society, may be considered strong evidence that persons of skill in the art regarded the work corresponding to the claimed invention to be original and new.

As there is no evidence that any work published or otherwise in the public domain disclosed or suggested the presently claimed invention, withdrawal of the rejection of claims 18-35 under 35 U.S.C. §102(b) as allegedly being anticipated by Hertel *et al.*, Nitecki et al., Watasuka et al., or WO 98/50420, is respectfully requested.

III. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,
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